dry pyridine there was added 14.4 g. (0.08 mole) of *o*-sulfobenzoic anhydride. The solution was poured into 600 ml. of acetone and the precipitated pyridine salt was filtered. The crude salt was recrystallized twice from water with one decolorization with carbon, m. p. 243°.

Anal. Calcd. for $C_{22}H_{19}O_6N_5S_2$: C, 51.50; H, 3.71. Found: C, 51.70; H, 3.70.

The pyridine salt was suspended in water and sodium hydroxide was added to *p*H 7.2. The pyridine was removed, and the solution concentrated to a sirup under reduced pressure. Absolute alcohol was added, and the mixture again concentrated under reduced pressure. The precipitated salt was filtered and washed with 95% alcohol and dried. Analysis showed the product to be a mixture of the mono- and di-sodium salts.

Anal. Calcd. for $C_{17}H_{12}O_6N_4S_2Na_2 \cdot H_2O$: C, 41.40; H, 2.82; Na, 9.28. Found: C, 40.70; H, 2.97; Na, 8.54.

The mono-sodium salt was prepared by treating the pyridine salt with two equivalents of sodium hydroxide and evaporating the resulting solution to dryness. The solid material was dissolved in a small volume of water and acidified to *p*H 3.8 with hydrochloric acid. The material which crystallized was recrystallized twice from aqueous alcohol. The product proved to be the monohydrate even after being dried at 110°. The theoretical amount of water was removed by drying at 110° and 3 mm. pressure, yield 76%.

Anal. Calcd. for $C_{17}H_{13}O_6N_4S_2Na \cdot H_2O$: C, 43.10; H, 3.18; N, 11.81; Na, 4.85; H_2O, 3.80. Found: C, 43.27; H, 3.12; N, 11.65; Na, 4.83; H_2O, 3.87.

N⁴-Sodium-β-sulfopropionylsulfanilamide.—A suspension of 35 g. (0.2 mole) of sulfanilamide in 50 ml. of dry pyridine was treated with 25 g. (0.18 mole) of β-sulfopropionic anhydride. A reaction occurred with the liberation of considerable heat. The reaction mixture was poured slowly into 600 ml. of acetone with constant stirring. The pyridine salt separated and was recrystallized from 95% ethanol; yield was 23.6 g. (33.8%), m. p. 185–186°.

Anal. Calcd. for $C_{14}H_{17}O_6N_3S_2$: C, 43.40; H, 4.39; S, 16.52. Found: C, 43.20; H, 4.22; S, 16.40.

A solution of 16 g. of the pyridine salt in water was adjusted to *p*H 7.0 with sodium hydroxide. The solution was evaporated nearly to dryness under reduced pressure. A portion of 95% ethanol was added, and the evaporation repeated. The solid material was crystallized twice from 95% alcohol. Yield was 12 g. (88%).

Anal. Calcd. for $C_9H_{11}O_6N_2S_2Na$: C, 32.72; H, 3.36; N, 8.47; Na, 6.96. Found: C, 32.75; H, 3.29; N, 8.46; Na, 7.02.

N⁴-Sodium-β-sulfopropionylsulfathiazole.—A suspension of 225 g. (1 mole) of sulfathiazole in 500 ml. of dry pyridine was treated with an equivalent amount (136 g.) of β-sulfopropionic anhydride. When the addition was complete, the hot solution was kept at 80° for two hours and then added to 2 liters of benzene. The benzene extract was decanted from the sirup, which was air dried and extracted with hot water. Considerable unreacted sulfathiazole did not dissolve and was removed by filtration after the solution had cooled. The filtrate was decolorized with carbon and evaporated to dryness under reduced pressure. The sirup was recrystallized from twice its volume of alcohol, m. p. 210–215° dec.

Anal. Calcd. for $C_{17}H_{18}O_6N_4S_3$: C, 43.40; H, 3.83. Found: C, 43.30; H, 3.71.

The pyridine salt was converted to the sodium salt by treating the aqueous solution with sodium hydroxide to *p*H 7.2. One mole of pyridine salt required 1.25 mole of sodium hydroxide. The product crystallized out in part, and the remainder was obtained from the mother liquors by evaporation to dryness. The residue thus obtained was recrystallized from water.

Anal. Calcd. for $C_{12}H_{12}O_6N_3S_3Na$: C, 34.90; H, 2.93; N, 10.16; Na, 5.56. Found: C, 34.85; H, 2.88; N, 10.08; Na, 5.56.

Summary

1. The preparation of some N⁴-tartaryl and diacetyltartarylsulfonamides by the action of diacetyltartaric anhydride on the sulfonamide in pyridine or glacial acetic acid has been described.

2. The *o*-sulfobenzoyl derivatives of sulfanilamide, sulfathiazole and sulfadiazine have been prepared.

3. A method has been described for the preparation of the β-sulfopropionic acid derivatives of sulfanilamide and sulfathiazole.

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[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. XV. Amides of Pantoyltaurine[1]

BY R. WINTERBOTTOM, J. W. CLAPP, W. H. MILLER, J. P. ENGLISH AND R. O. ROBLIN, JR.

Since the demonstration by McIlwain and Hawking[2] that pantoyltaurine[3] acted as a therapeutic agent in rats infected with a lethal strain of hemolytic streptococcus, numerous papers[4] have appeared describing the preparation and antibacterial activity of other pantothenic acid analogs. None of these appears to show consistently greater bacteriostatic action *in vitro* than pantoyltaurine. Only one, 2-(pantoylamino)-ethyl-4-aminophenyl sulfone,[5] has been found to be active *in vivo*. In this case, as with pantoyltaurine, administration of the compound by repeated subcutaneous injection was necessary to attain a therapeutic effect. Although pantoyltaurine was shown to be inactive against *Plasmodium relictum* infection in the canary,[2] the work of Trager[6] suggested that pantothenic acid might be a growth

(1) Presented in part before the Division of Medicinal Chemistry, Atlantic City Meeting of the American Chemical Society, April 10, 1946.

(2) McIlwain and Hawking, *Lancet*, **244**, 449 (1943).

(3) The abbreviated term "pantoyl" is used for the radical "α,γ-dihydroxy-β,β-dimethylbutyryl."

(4) *Cf.* Roblin, *Chem. Rev.*, **38**, 255 (1946).

(5) Madinaveitia, Martin, Rose and Swain, *Biochem. J.*, **39**, 85 (1945).

(6) Trager, *J. Expil. Med.*, **77**, 411 (1943).

TABLE I

AMIDES OF PANTOYLTAURINE

$CH_2OHC(CH_3)_2CHOHCONH-CH_2CH_2SO_2N(R_1)(R_2)$

No.	Configuration	R_1	R_2	M. p., °C. (cor.)	$[\alpha]^{T^a}D$	Antimalarial activity[b] quinine equiv.
1	*d*	Me	Me	B. p. 116 (10^{-4})	+23	
2	*dl*	H	2-Pyridyl	141–142		
3	*d*	H	2-Pyridyl[f]	124.1–125.6	+39	0.25
4	*l*	H	2-Pyridyl	124.1–126.1	−38	
5	*d*	H	2-Pyridyl (diacetate of No. 3)	133–134.5	+15	
6	*d*	H	5-Chloro-2-pyridyl	156–157	+35	1
7	*d*	H	5-Bromo-2-pyridyl	159–160	+30	1 (0.5)
8	*d*	H	2-Pyrimidyl[f]	186–188	+24[g]	
9	*d*	H	5-Chloro-2-pyrimidyl	186–188	+32	1
10	*d*	H	5-Bromo-2-pyrimidyl	185–187	+24[h]	
11	*d*	H	2-Quinolyl[f]		+26	
12	*d*	H	Phenyl	108–109	+40	12 (2)
13	*d*	H	4-Chlorophenyl	110–111.5[i]	+37	16 (4)
14	*dl*	H	3,5-Dibromophenyl	87–89		
15	*d*	H	3,5-Dibromophenyl	124.6–126.6	+26	0.5
16	*l*	H	3,5-Dibromophenyl	123.6–125.6	−24	
17	*d*	H	4-Tolyl	95.5–97	+39	4 (2)
18	*dl*	H	4-Sulfamylphenyl	166.5–167.5		0.5 (0.3)
19	*d*	H	4-Methoxyphenyl	110–111.5	+36	2 (0.5)
20	*d*	H	4-Carboxyphenyl	162–163[k]	+35	
21	*d*	H	4-Nitrophenyl	152–152.5	+39	(1)
22	*d*	H	4-Aminophenyl	139–140.5	+36	
23	*d*	Et	Phenyl	116.5–118	+36	0.5
24	*d*	H	2-Naphthyl	155–156	+35	0.5
25	*d*	H	Benzyl	93.5–94.5	+34	(0.5)

factor for this organism.[7] It appeared to us that pantothenic acid antagonists with better absorption–excretion characteristics than pantoyltaurine, making oral administration possible, would be of possible use in the chemotherapy of malaria and certain bacterial infections.

We have prepared a number of substituted amides of pantoyltaurine, the metabolite and anti-metabolite having the same structural relationship as that existing between *p*-aminobenzoic acid and the sulfanilamides.

$$CH_2OH-C(CH_3)_2-CHOH-CONHCH_2CH_2\begin{cases}-COOH\\-SO_2NHR\end{cases}$$

$$C_6H_4\begin{matrix}CO\\CO\end{matrix}NCH_2CH_2SO_3K \longrightarrow RSO_2Cl \longrightarrow$$

(I) (II)

$$RSO_2NHR' \longrightarrow NH_2CH_2CH_2SO_2NHR'$$

(III) (IV)

Taurine was condensed with phthalic anhydride to form the potassium salt of 2-phthalimidoethanesulfonic acid (I), which was then converted to 2-phthalimidoethanesulfonyl chloride (II). The sulfonyl chloride reacted with both heterocyclic and isocyclic amines to form the corresponding 2-phthalimidoethanesulfonamides (III). The weakly basic amines, 2-amino-5-chloropyrimidine and 2-amino-5-bromopyrimidine, did not react. However, the halogenation of 2-(2-phthalimidoethylsulfonamido)-pyrimidine (no. 5a) in acetic acid solution gave excellent yields of the desired 5-halopyrimidines (nos. 6a and 7a).

Cleavage of the phthaloyl derivatives to the corresponding 2-aminoethanesulfonamides (IV) was effected by the method of Ing and Manske.[8]

Taurinamide-(2-aminoethanesulfonamide) and 2-(2-aminoethylsulfonamido)-pyridine were also synthesized by the steps

$$C_6H_5CONHCH_2CH_2SO_3H \longrightarrow$$

(V)

$$C_6H_5CONHCH_2CH_2SO_2Cl + C_6H_5\overset{Cl}{\underset{|}{C}}{=}NCH_2CH_2SO_2Cl$$

(VI) (VII)

Thionyl chloride reacted with 2-benzamidoethanesulfonic acid (V) to form predominantly 2-benzamidoethane-sulfonyl chloride (VI). Concomitantly some N-(2-chlorosulfonylethyl)-benzimidyl chloride (VII) was formed. Ammonia and 2-aminopyridine reacted normally with VI to give respectively 2-benzamidoethanesulfonamide and 2-(2-benzamidoethylsulfonamido)-pyridine. Hydrolytic removal of the benzoyl group gave the 2-aminoethanesulfonamides. The imino chloride

(7) Recently Mead, Rapport, Senear, Maynard and Koepfli, *J. Biol. Chem.*, **163**, 465 (1946), described the preparation of *d*-pantoyltaurylamide (*d*-(2-pantoylamino)-ethanesulfonamide) and several heterocyclic and other derivatives. They reported that *d*-pantoyltaurylamide showed definite activity *in vivo* in the suppression of malaria parasites under certain test conditions.

(8) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

TABLE I (*Continued*)

AMIDES OF PANTOYLTAURINE

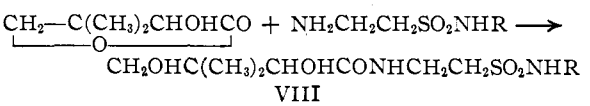
Antistreptococcal activity Group A *in vitro*[c] bacterial index	Strain C 203 *in vivo* SD 50[d] g./kg.	Formula	Carbon, % Calcd.	Found[e]	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
3200		$C_{10}H_{22}N_2O_5S$	42.5	40.9	7.9	7.9	9.9	10.0
200		$C_{13}H_{21}N_3O_5S$	47.1	47.0	6.4	6.2	12.7	12.8
100	0.5	$C_{13}H_{21}N_3O_5S$	47.1	47.1	6.4	6.6	12.7	12.6
>6400		$C_{13}H_{21}N_3O_5S$					12.7	12.6
>6400	.7	$C_{17}H_{25}N_3O_7S$	49.1	49.0	6.1	6.2	10.1	10.0
25	.5	$C_{13}H_{20}ClN_3O_5S$	42.7	42.9	5.5	5.5	11.5	11.3
25	.5	$C_{13}H_{20}BrN_3O_5S$	38.1	38.1	4.9	5.0	10.4	10.4
50	.5	$C_{12}H_{20}N_4O_5S$	43.4	43.4	6.1	6.1	16.9	17.1
25	.5	$C_{12}H_{19}ClN_4O_5S$	39.3	39.4	5.2	5.5	15.3	15.2
25	.6	$C_{12}H_{19}BrN_4O_5S$	35.1	35.2	4.7	4.9	13.6	13.5
200	.6	$C_{17}H_{23}N_3O_5S$	53.5	52.7	6.1	6.5	11.0	10.6
25	.6	$C_{14}H_{22}N_2O_5S$	50.9	51.0	6.7	6.9	8.5	8.4
25	.3	$C_{14}H_{21}ClN_2O_5S$	46.1	46.3	5.8	5.8	7.7	7.4
		$C_{14}H_{20}Br_2N_2O_5S$	34.4	34.4	4.1	4.2	5.7	5.7
12	.2	$C_{14}H_{20}Br_2N_2O_5S$	34.4	34.2	4.1	4.0	5.7	5.6
> 800		$C_{14}H_{20}Br_2N_2O_5S$					5.7	5.5
100	.5	$C_{15}H_{24}N_2O_5S$	52.3	52.4	7.0	7.1	8.1	8.4
25	>1.6	$C_{14}H_{23}N_3O_7S_2$	41.1	40.9	5.7	5.7	10.3	10.2
400	0.6	$C_{15}H_{24}N_2O_6S$	50.0	49.9	6.7	6.7	7.8	7.6
6400	>1.6	$C_{15}H_{22}N_2O_7S$	48.1	48.6	5.9	6.0	7.5	7.4
25	0.4	$C_{14}H_{21}N_3O_7S$	44.8	44.8	5.6	5.7	11.2	11.1
800	>1.6	$C_{14}H_{23}N_3O_5S$	48.7	48.7	6.7	6.9	12.2	12.1
50	0.9	$C_{16}H_{26}N_2O_5S$	53.6	53.8	7.3	7.1	7.8	7.8
50	.7	$C_{18}H_{24}N_2O_5S$	56.8	56.9	6.4	6.4	7.4	7.5
3200	>1.6	$C_{15}H_{24}N_2O_5S$	52.3	52.3	7.0	7.0	8.1	8.3

[a] Unless otherwise noted in 95% ethanol, C = 1–2%, temp., 22–30°. [b] Trophozoite-induced *P. gallinaceum* infection in chicks. Unbracketed values for a test in which the peak parasitemia in the controls occurred seven days after infection; bracketed values, four days. [c] The antibacterial index is the minimum value for the ratio of analog to pantothenic acid required for complete inhibition. [d] SD 50, the median survival dose, determined in mice: Single oral dose administered at time of infection. [e] Microanalyses were performed under the direction of Dr. J. A. Kuck of these Laboratories. [f] Previously prepared by Mead, *et al.* (ref. 7). [g] Water, C = 2.83 g. [h] Water, C = 0.40 g. [i] When recrystallized from benzene, an apparently dimorphic form melting at 101–103° is obtained. [k] Obtained if determined rapidly. The melt resolidifies and decomposes at 250°. Apparently dissociation to 2-aminoethylsulfonanilide occurs on heating. [l] Amorphous solid.

(VII) when allowed to react with ammonia and 2-aminopyridine underwent cyclization to form substituted 5,6-dihydro-1,2,4-thiadiazine derivatives.

Of the two optical isomers of pantothenic acid, only the naturally occurring dextro form is biologically active. Snell[9] and Kuhn, *et al.*,[10] demonstrated a similar relationship in the case of pantoyltaurine. Since *d*-pantolactone (α,γ-dihydroxy-β,β-dimethylbutyrolactone) was available,[11] the *d*-2-(pantoylamino)-ethylsulfonamides (Table I) were synthesized rather than the racemates. The levo isomers (no. 4 and 16) were prepared from *l*-pantolactone.

Two methods were found efficacious in condensing pantolactone with the 2-aminoethanesulfonamides. The potassium salts of the sulfonamides reacted readily with the lactone in alcohol solution to form the desired pantothenic acid analogs (VIII).



$$CH_2{-}C(CH_3)_2CHOHCO + NH_2CH_2CH_2SO_2NHR \longrightarrow CH_2OHC(CH_3)_2CHOHCONHCH_2CH_2SO_2NHR$$

VIII

For 2-aminoethylsulfonamides melting below 180°, fusion with the lactone for one or two hours was found preferable.

Several analogs were prepared in which the pantoyl moiety was replaced by a butyryl or hydroxylated butyryl group. Butyric anhydride reacted with β-alanine and taurine to give N-butyryl-β-alanine and N-butyryltaurine, respectively. Condensation of γ-butyrolactone with the sodium salts of β-alanine and taurine, by fusion, gave the corresponding γ-hydroxybutyryl compounds. None showed biological activity comparable to the analogs containing the pantoyl group intact.

Biological Activity (Table I).—The amides of pantoyltaurine, with few exceptions, possess both antibacterial[12] and antiplasmodial activity.[13]

(9) Snell, *J. Biol. Chem.*, **139**, 975 (1941); **141**, 121 (1941).

(10) Kuhn, Wieland and Möller, *Ber.*, **74**, 1605 (1941).

(11) We are indebted to Dr. S. H. Babcock of Lederle Laboratories, Inc., for a generous supply of *d*, *l*, and *dl*-pantolactone.

(12) White, *et al.*, to be published.

(13) Brackett, Waletzky and Baker, *J. Parasitol.*, **32**, 453 (1946).

Against *Streptococcus hemolyticus*, strain C 203, they exhibited a much greater *in vitro* antistreptococcal activity than pantoyltaurine. Of the other pathogenic bacteria tested, only *Streptococcus viridans*, *Streptococcus agalactiae* and pneumococcus proved sensitive. With the four analogs tested (nos. 3, 6, 10 and 12) the antibacterial activity could be competitively nullified by pantothenic acid, proving the mode of action, in these cases, to be inhibition of the utilization of pantothenic acid.

The dextro form of pantoyltaurine has been shown to be ten to thirty times more active than the levo form against *L. arabinosus* and *Streptobacterium plantarum*. The activity of the levo form was ascribed to its contamination by the biologically active isomer.[10] The total activity of the dibromoanilide (no. 15) may be the result of two modes of action, an antipantothenate activity and a "dibromoaniline activity."[14] At high concentrations the antibacterial action of no. 15 is not completely reversed by pantothenate. The levo isomer, no. 16, which might be expected to retain the "dibromoaniline activity," but not the antipantothenate activity, was prepared and found to be inhibitory at essentially the same concentration as the dextro form in the presence of added pantothenate (Table II). The levo isomer, no. 4, of the pantothenate-reversible *d*-2-[2-(pantoylamino)-ethylsulfonamido]-pyridine showed no activity at high concentrations. This is not only confirmatory evidence for the optical purity of both isomers but also demonstrates that the levo forms of pantothenic acid analogs are biologically inactive with respect to the vitamin.

TABLE II

ANTIBACTERIAL ACTIVITY OF OPTICAL ISOMERS

Compound[c]	M. E. C.[a] of compound in presence of pantothenic acid 0.02 mg. % P. A.[b]	128 mg. % P. A.
d-PS-3,5-dibromoanilide	1/8	64
l-PS-3,5-dibromoanilide	32	64
d-2-PS-pyridine	1	>128
l-2-PS-pyridine	>128	...

[a] The minimum concentration in mg. per cent. necessary for complete inhibition of growth; test organism is Strep. C-203. [b] P.A. = pantothenic acid. [c] PS = 2-(pantoylamino)-ethylsulfono- (or sulfonamido-).

When administered orally in a single dose, many of the analogs, unlike pantoyltaurine, gave therapeutically effective blood levels.[15] Compounds no. 13 and 15 gave the best maintained blood levels and also proved superior, on a dosage basis, in saving mice infected with *Streptococcus hemolyticus*, strain C 203. The *in vivo* activity could also be nullified by the oral administration of supplementary pantothenic acid to the mice.

Fifteen of the analogs were tested against blood-induced *Plasmodium gallinaceum* infection in the chick. The drug was incorporated in the diet. When small inocula were used so that peak parasitemias were not reached until seven days after infection, all showed some activity and some were more active than quinine. With the less sensitive but more commonly used infection requiring four days to reach peak parasitemias, the most active compound, no. 13, was at least four times as active as quinine. These compounds are markedly superior to pantoyltaurine, which showed no activity when given in large doses intraperitoneally. Since comparative blood levels were not determined, it is not known whether the differences in activity were caused by variation in inherent antimalarial activity or in pharmacological characteristics. Incorporation of supplementary pantothenic acid in the diet nullified the activity.

(14) Goetchius and Lawrence, *J. Bact.*, **49**, 575 (1945).

(15) A microbiological assay has been devised by Mrs. E. R. Jackson of these Laboratories.

Experimental[16]

2-Benzamidoethanesulfonyl Chloride.—Finely powdered 2-benzamidoethanesulfonic acid[17] weighing 48.8 g. (0.213 mole) was divided into two equal portions, each of which was treated with 52 cc. (0.716 mole) of thionyl chloride. The mixtures were heated at 50° for eight hours with occasional shaking. Although unreacted starting material remained undissolved, the reaction was stopped by the addition of 100 cc. of benzene to each flask. The batches were combined and refrigerated overnight. The benzene and thionyl chloride were then removed by vacuum distillation from a warm water-bath at 40°. The residue was triturated with dry benzene which was then removed by vacuum distillation. This process was repeated. The residue was dissolved in hot benzene and filtered from 15 g. of 2-benzamidoethanesulfonic acid. The filtrate was concentrated as above and the residue leached with three portions of boiling petroleum ether. This removed N-(2-chlorosulfonylethyl)-benzimidyl chloride. A yield of 33.3 g. of product melting at 81–86° remained undissolved. Recrystallization from benzene gave pure material, m. p. 87.5–89°.

Anal. Calcd. for $C_9H_{10}ClNO_3S$: C, 43.6; H, 4.0; Cl, 14.3. Found: C, 43.5; H, 4.3; Cl, 14.4.

N-(2-Chlorosulfonylethyl)-benzimidyl Chloride.[18]—A mixture of 4.0 g. of 2-benzamidoethanesulfonic acid and 8.0 cc. of thionyl chloride was refluxed for fifteen minutes. After the addition of 20 cc. of benzene, the reaction mixture was vacuum concentrated. Another portion of benzene was added and distilled off to remove any remaining

(16) All melting points are corrected.

(17) Josephson, *Biochem. Z.*, **264**, 441 (1933).

(18) **1,1-Dioxo-3-phenyl-5,6-dihydro-1,2,4-thiadiazine.**—A vigorous reaction occurred when 21.8 g. (0.0824 mole) of N-(2-chlorosulfonylethyl)-benzimidyl chloride was added to 110 cc. of concentrated ammonium hydroxide solution. A crude yield of 15.8 g. (92%) of product resulted by cooling and subsequent concentration of the filtrate. Several recrystallizations from absolute alcohol gave pure material, m. p. 214–214.5° (cor.). When subjected to hydrolysis with 20% hydrochloric acid for eighty minutes benzoic acid and taurinamide hydrochloride (83% yield) were isolated. *Calcd.* for $C_9H_{10}N_2O_2S$: C, 51.5; H, 4.8; N, 13.3. Found: C, 51.8; H, 5.0; N, 13.1.

1,1-Dioxo-3-phenyl-2(2-pyridyl)-5,6-dihydro-1,2,4-thiadiazine.—A solution of 2.0 g. (0.0075 mole) of N-(2-chlorosulfonylethyl)-benzimidyl chloride in 2.0 cc. of acetone was added to 2.4 g. (0.023 mole) of 2-aminopyridine dissolved in 10 cc. of acetone. The solution grew warm and deposited an oil. After standing overnight at room temperature, the acetone was evaporated *in vacuo* and the residue treated with 15.0 cc. of water. The 0.65 g. of crude product when recrystallized twice from absolute ethanol melted at 176–177° (cor.). *Calcd.* for $C_{14}H_{13}N_3O_2S$: C, 58.6; H, 4.5; N, 14.7. Found: C, 58.6; H, 5.0; N, 14.8.

thionyl chloride. The semi-crystalline residue was leached with two 50-cc. portions of boiling petroleum ether (b. p. 30–60°). On cooling the petroleum ether solution in a Dry Ice-bath, 2.0 g. of crude product was obtained. After recrystallizing twice from petroleum ether a melting point of 35–38° was obtained. It is very readily hydrolyzed by atmospheric water vapor and satisfactory chlorine analyses could not be obtained. Calcd. for $C_9H_9Cl_2NO_2S$: Cl, 26.7. Found: Cl, 24.7.

2-Benzamidoethanesulfonamide.—A. Five grams (0.0202 mole) of 2-benzamidoethanesulfonyl chloride was added portionwise to 25 cc. of concentrated ammonium hydroxide. After standing one hour the precipitate was filtered and dried, yielding 3.7 g. (80%) of crude product; m. p. 159–162°. Two recrystallizations from ethanol gave 3.2 g. of pure product, m. p. 168–170°.

B. A mixture of 2.14 g. (0.0133 mole) of 2-aminoethanesulfonamide hydrochloride and 6.0 cc. of dry pyridine was heated to 70°. With stirring, 1.54 cc. (0.0133 mole) of benzoyl chloride was added in three portions at five-minute intervals. The temperature rose to 90° after each addition. The mixture was held at 70° for an additional fifteen minutes, cooled and poured into 60 cc. of cold water. The white crystalline precipitate when filtered and dried weighed 2.33 g., m. p. 168–171°. Recrystallization gave 2.1 g. of pure product, m. p. 169.5–170.5°. A mixed melting point with material obtained from the sulfonyl chloride gave no depression. Calcd. for $C_9H_{12}N_2O_3S$: C, 47.4; H, 5.3; N, 12.3. Found: C, 47.8; H, 5.2; N, 12.4.

2-Aminoethanesulfonamide Hydrochloride (no. 1b).—A mixture of 12.3 g. (0.054 mole) of 2-benzamidoethanesulfonamide and 230 cc. of 20% hydrochloric acid was refluxed for two hours. The cooled solution was filtered to remove benzoic acid, concentrated, filtered again and concentrated to dryness. The crude product was recrystallized by refluxing for three hours with two 250-cc. portions of absolute ethanol. The combined alcohol solutions deposited 5.6 g. (64%) of product, m. p. 130–134°.

2-(2-Benzamidoethylsulfonamido)-pyridine.—To 43 g. (0.174 mole) of 2-benzamidoethanesulfonyl chloride dissolved in 140 cc. of dry acetone was added with shaking a solution of 40.4 g. (0.43 mole) of 2-aminopyridine in 140 cc. of acetone. The mixture grew warm and an oil separated. The mixture was warmed on the steam-bath for ten minutes with occasional shaking. After standing for two days at room temperature, the acetone was removed *in vacuo* and the residue treated with water. The gummy residue changed to a white solid which was filtered off. The resultant 26.0 g. (49%) of crude product melted at 165–180°. Recrystallization from ethanol or water gave pure material melting at 180.5–181.5°. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.1; H, 4.9; N, 13.8. Found: C, 55.1; H, 5.0; N, 13.9.

2-(2-Aminoethylsulfonamido)-pyridine Hydrochloride (no. 3b).—A solution of 26 g. (0.085 mole) of 2-(2-benzamidoethylsulfonamido)-pyridine in 500 cc. of 1.25 *N* sodium hydroxide was refluxed for four hours. The cooled reaction mixture was filtered and adjusted to *p*H 6. On standing one hour, 3.0 g. of unreacted starting material precipitated. The filtrate was adjusted to *p*H 3 with hydrochloric acid, concentrated to a small volume, and filtered from 9.3 g. of benzoic acid. Further concentration yielded a crystalline residue which was refluxed with 500 cc. of absolute ethanol, filtered hot to remove salt and concentrated to 250 cc. After seeding and refrigerating for two days, 14.8 g. of product, m. p. 166–169°, was obtained.

Potassium Salt of 2-Phthalimidoethanesulfonic Acid.[19]—A stirred suspension of 169.6 g. (1.36 moles) of finely pulverized taurine[20] and 142 g. (1.45 moles) of anhydrous potassium acetate in 475 cc. of acetic acid was refluxed for ten minutes and treated with 214 g. (1.45 moles) of phthalic anhydride. The mixture was refluxed with stirring for two and one-half hours. During this period the reaction mixture became almost free of undissolved solids followed by precipitation of the product. After cooling in an ice-bath with continued stirring, the white product was filtered off and washed on the funnel with acetic acid and 2B alcohol. The yield of 357 g. (90%) was sufficiently pure for further use. A small amount of water-insoluble impurity was present which could be removed by crystallization from 720 cc. of water. When dried at 110°, pure product weighing 323 g. (81%) was obtained.

2-Phthalimidoethanesulfonyl Chloride.—The preparation of large amounts of this compound was found to occur in better yield when conducted in benzene solution rather than by heating a mixture of the dry reactants as previously described.[21,22] A suspension of 440 g. (1.5 moles) of finely powdered potassium salt of 2-phthalimidoethanesulfonic acid in 2.2 liters of benzene was prepared. With stirring (Hershberg stirrer), 400 cc. of benzene was distilled off to remove any water present. The mixture was treated with 225 g. (1.32 moles) of phosphorus pentachloride and stirred under reflux on a steam-bath for one hour. Another 225 g. of pentachloride was then added and the reaction continued for an additional ninety minutes. The benzene and phosphorus oxychloride were then removed by vacuum distillation from a warm water-bath. The moist crystalline residue was stirred with about 2 kg. of crushed ice and filtered. The gray filter cake was resuspended in cold water, stirred and filtered. After further washing with water, the crude product was air dried overnight. The resultant 400 g. was recrystallized from 950 cc. of ethylene chloride, yielding 354 g. (90%) of product melting at 159–162°.

2-Phthalimidoethanesulfonamide.—The following procedure gave better yields than the previously described[23] method using aqueous ammonium hydroxide. To 200 g. of liquid ammonia in a Dewar flask was added 87.5 g. (0.32 mole) of 2-phthalimidoethanesulfonyl chloride in the course of thirty minutes. After stirring for an additional thirty minutes, the ammonia was allowed to evaporate in a beaker. The viscous residue was stirred with 100 cc. of water containing 60 cc. of acetic acid. The resultant warm slurry was chilled and filtered. After washing with water on the funnel and drying at 100°, 60.3 g. of product melting at 209–212° was obtained. The filtrate on standing overnight deposited an additional 7.0 g., melting at 197–201°. In a repetition of this experiment, the reaction mixture was allowed to stand overnight in the Dewar flask. Apparently enough atmospheric moisture was absorbed to cause hydrolysis of the product to the water soluble ammonium salt of the corresponding phthalamic acid. However, upon refluxing the aqueous solution for two hours after acidification with acetic acid, an 87% yield of product resulted.

2-Phthalimidoethylsulfonyl Dimethylamide (no. 1a).—To 125 cc. of redistilled dimethylamine, cooled in a bath at −15°, was added 27.4 g. (0.10 mole) of 2-phthalimidoethanesulfonyl chloride with stirring. The reaction product was isolated (87%) by a procedure similar to that used for 2-phthalimidoethanesulfonamide.

Condensation of 2-Phthalimidoethanesulfonyl Chloride with Aromatic Amines. Procedure A.—In general one mole of the acid chloride was added in portions to 1–2 moles of the amine dissolved or suspended in 10 moles of dry pyridine. The reaction mixture was stirred and cooled in an ice-bath during the addition and for an additional half hour. The external cooling was then discontinued and the mixture stirred for an additional hour at room temperature. In many cases, the product crystallized from the reaction mixture, forming a thick paste so that the use of a Hershberg stirrer was necessary to get adequate mixing. With aniline, substituted anilines and 2-aminonaphthalene highly colored reaction mixtures, usually red or purple, resulted. The heterocyclic amines, with the exception of the 2-amino-5-halogenopyridines,

(19) Vanags and Veinbergs, *Ber.*, **75**, 1558 (1942).

(20) Goldberg, *J. Chem. Soc.*, 4 (1943).

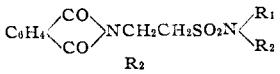
(21) Christiansen, U. S. Patent 2,184,279; *C. A.*, **34**, 2536 (1940).

(22) Gabriel and Colman, *Ber.*, **44**, 3629 (1911).

(23) Miller, Sprague, Kissinger and McBurney, THIS JOURNAL, **62**, 2099 (1940).

TABLE III

2-PHTHALIMIDOETHANESULFONAMIDES[a]



No.	R_1	R_2	M. p., °C. (cor.)	Empirical formula	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
1a	Me	Me	154.5–156	$C_{12}H_{14}N_2O_4S$	9.9	9.7				
2a	H	2-Pyridyl[b]	215–217	$C_{15}H_{13}N_3O_4S$	12.7	12.5	54.4	54.8	4.0	4.0
3a	H	5-Chloro-2-pyridyl	198.5–199	$C_{15}H_{12}ClN_3O_4S$	8.8[c]	8.9				
4a	H	5-Bromo-2-pyridyl	205–206	$C_{15}H_{12}BrN_3O_4S$	7.8[c]	7.9	43.9	44.4	2.9	3.2
5a	H	2-Pyrimidyl[b]	251–253	$C_{14}H_{12}N_4O_4S$	16.9	16.8	50.6	50.6	3.6	3.7
6a	H	5-Chloro-2-pyrimidyl	250–253 (dec.)	$C_{14}H_{11}ClN_4O_4S$	9.7[d]	9.9				
7a	H	5-Bromo-2-pyrimidyl	261–264 (dec.)	$C_{14}H_{11}BrN_4O_4S$	13.6	13.7				
8a	H	2-Pyrazinyl	205–207	$C_{14}H_{12}N_4O_4S$	16.9	16.4				
9a	H	2-Thiazolyl[b]	228.5–231 (dec.)	$C_{13}H_{11}N_3O_4S_2$	19.0[c]	18.9				
10a	H	2-(1,3,4-Thiadiazolyl)	249.5–251.5 (dec.)	$C_{12}H_{10}N_4O_4S_2$	19.0[c]	19.1				
11a	H	Phenyl[e]	141–143	$C_{16}H_{14}N_2O_4S$	8.5	8.3				
12a	H	4-Chlorophenyl	154–155	$C_{16}H_{13}ClN_2O_4S$	7.7	7.6				
13a	H	3,5-Dibromophenyl	208–210	$C_{16}H_{12}Br_2N_2O_4S$	5.7	5.8				
14a	H	4-Tolyl[e]	168–170	$C_{17}H_{16}N_2O_4S$	8.1	8.2	59.3	59.4	4.7	4.6
15a	H	4-Sulfamylphenyl[f]	250–254	$C_{16}H_{15}N_3O_6S_2$	10.3	10.0				
16a	H	4-Methoxyphenyl	148–149	$C_{17}H_{16}N_2O_5S$			56.7	56.6	4.5	4.7
17a	H	4-Carbethoxyphenyl	183–184	$C_{19}H_{18}N_2O_6S$			56.7	57.0	4.5	4.8
18a	H	4-Carboxyphenyl	251–251.5 (dec.)	$C_{17}H_{14}N_2O_6S$			54.5	54.4	3.8	4.1
19a	H	4-Nitrophenyl	214.5–215.5	$C_{16}H_{13}N_3O_6S$			51.2	51.4	3.5	3.7
20a	Et	Phenyl	149–150.5	$C_{18}H_{18}N_2O_4S$	7.8	7.3				
21a	H	2-Naphthyl	236–236.5	$C_{20}H_{16}N_2O_4S$			63.1	63.4	4.2	4.4
22a	H	Benzyl[g]	139.5–141	$C_{17}H_{18}N_2O_5S$	7.7	7.6				
23a	H	2-Quinolyl	200–203	$C_{19}H_{15}N_3O_4S$	11.0	11.3				

[a] Unless otherwise noted, these compounds were recrystallized from acetic acid or aqueous acetic acid. [b] Previously prepared by Mead, *et al.* (Ref. 7). [c] Sulfur analyses. [d] Chlorine analyses. [e] Recrystallized from ethanol. [f] No suitable solvent for recrystallization could be found. The analytical sample was obtained by precipitation from a basic solution by aqueous acetic acid. [g] Actually the phthalamic acid, N-[2-(benzylsulfamyl)-ethyl]-phthalamic acid.

gave less highly colored reaction mixtures. After completion of the reaction, the mixture was poured into dilute hydrochloric acid with stirring. The precipitated product, after washing with water, was recrystallized from acetic acid or aqueous acetic acid. The yields varied from 50 to 95% depending upon the amine employed. With the exceptions indicated below, this procedure was used in preparing all of the substituted 2-phthalimidoethanesulfonamides listed in Table III.

2-(2-Phthalimidoethylsulfonamido)-thiazole (no. 9a).—The condensation of the acid chloride with equivalent amounts of 2-aminothiazole or 2-amino-1,3,4-thiadiazole led to a mixture of mono- and di-substituted products. Increasing the proportion of amine suppressed di-substitution, but not completely. Separation of the two products depended upon the solubility of the desired mono-substituted product in cold dilute ammonium hydroxide solution.

Using Procedure A, 37.5 g. of a mixture of both possible products was obtained from 30 g. (0.30 mole) of 2-aminothiazole and 32.9 g. (0.12 mole) of 2-phthalimidoethanesulfonyl chloride. The mixture was pulverized and stirred for fifteen minutes with 2.6 liters of ice-cold water containing 36.0 cc. of concentrated ammonium hydroxide. Most of the product dissolved. Filtration followed by acidification with hydrochloric acid yielded 25.5 g. of the mono-substituted product. Recrystallization from 1.6 liters of 25% acetic acid gave 22.9 g. of pure product.

Di-(2-phthalimidoethylsulfonyl)-2-aminothiazole.—By Procedure A, using equimolecular amounts of acid chloride and 2-aminothiazole, the crude product consisted mainly of the di-substituted compound. When 44.0 g. of the crude product was recrystallized from 730 cc. of 95% acetic acid, 26.6 g. of almost pure material, melting at 198–200°, was obtained. One of the substituents may be attached to the ring nitrogen. This possibility was not investigated. Calcd. for $C_{23}H_{18}N_4O_8S_3$: C, 48.1; H, 3.2; N, 9.8. Found: C, 48.2; H, 3.3; N, 9.7.

2-(2-Phthalimidoethylsulfonamido)-5-bromo(chloro)-pyrimidine (Nos. 6a and 7a).—To a boiling suspension of 45.0 g. of 2-(2-phthalimidoethylsulfonamido)-pyrimidine in 650 cc. of acetic acid was added 32 g. of bromine dissolved in 100 cc. of glacial acetic acid. The addition took forty-five minutes. The bromine was absorbed rapidly but no hydrogen bromide was evolved until about three-fourths of the bromine solution had been added. The starting material gradually dissolved and the product crystallized from the reaction mixture. When addition was completed, the reaction was continued for an additional hour. The product was then filtered from the cooled mixture. The light yellow filter cake was washed with two portions of acetic acid, several portions of hot water and finally methanol. When dried, the resultant 51 g. (91%) of white product, m. p. 255-260° dec., was recrystallized from 4 liters of acetic acid, yielding 47.5 g. of pure product.

Chlorination using a similar procedure gave a 61% yield of **2-(2-phthalimidoethylsulfonamido)-5-chloropyrimidine (No. 6a)**. Halogenation was shown to occur at position 5 of the pyrimidine ring by the isolation of 2-hydroxy-5-bromopyrimidine[24] when 2-(2-aminoethylsulfonamido)-5-bromopyrimidine was hydrolyzed with 65% sulfuric acid.

(2-Phthalimidoethylsulfono)-4-carboxyanilide (No. 18a).—Attempts to condense *p*-aminobenzoic acid with the sulfonyl chloride in pyridine solution were unsuccessful. Ethyl *p*-aminobenzoate reacted readily by Procedure A to give the ester which was hydrolyzed to the acid.

A solution of 87 g. (0.216 mole) of the ester (No. 17a) in 285 cc. of 2.5 *N* sodium hydroxide (0.71 mole) was heated for one hour on the steam-bath. After decolorization with Darco G-60, the solution was acidified to *p*H 2 with concentrated hydrochloric acid. The supernatant liquid was decanted from the precipitated gum which was

(24) English, Clark, Shepherd, Marson, Krapcho and Roblin, THIS JOURNAL, **68**, 1039 (1946).

TABLE IV

2-AMINOETHANESULFONAMIDES

$NH_2CH_2CH_2SO_2N(R_1)(R_2)$

No.	R_1	R_2	M. p., °C. (cor.)	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1b	H	H[a,f,j]	132.5–134	$C_2H_9ClN_2O_2S$	17.4	17.9				
2b	Me	Me[h,j]	144–145	$C_4H_{13}ClN_2O_2S$	14.9	14.7	25.5	25.7	7.0	6.9
3b	H	2-Pyridyl[e]	154–156	$C_7H_{11}N_3O_2S$	20.9	20.9	41.8	41.8	5.4	5.6
4b	H	2-Pyridyl[f,j]	170.5–171.5	$C_7H_{12}ClN_3O_2S$	18.1	18.0	35.4	35.3	5.1	5.5
5b	H	5-Chloro-2-pyridyl[d]	198.5–201.5	$C_7H_{10}ClN_3O_2S$	17.8	17.8				
6b	H	5-Chloro-2-pyridyl[f,j]	156–158	$C_7H_{11}Cl_2N_3O_2S$			30.9	31.1	4.1	4.2
7b	H	5-Bromo-2-pyridyl[d]	202–203 (dec.)	$C_7H_{10}BrN_3O_2S$	14.7	15.0				
8b	H	5-Bromo-2-pyridyl[f,j]	166–168	$C_7H_{11}BrClN_3O_2S$			26.6	26.7	3.5	3.6
9b	H	2-Pyrimidyl[b,d,k]	158–160	$C_6H_{10}N_4O_2S\cdot H_2O$	25.5	25.3	32.7	32.9	5.5	5.6
10b	H	2-Pyrimidyl[e,j]	215–218 (dec.)	$C_6H_{11}ClN_4O_2S$	23.5	23.3				
11b	H	5-Chloro-2-pyrimidyl[d]	208 (dec.)	$C_6H_9ClN_4O_2S$	23.7	23.3				
12b	H	5-Bromo-2-pyrimidyl[e]	215–217 (dec.)	$C_6H_9BrN_4O_2S$	19.9	20.0				
13b	H	5-Bromo-2-pyrimidyl[e,j]	263–264 (dec.)	$C_6H_{10}BrClN_4O_2S$	17.6	17.9				
14b	H	2-Pyrazinyl[d]	220–222 (dec.)	$C_6H_{10}N_4O_2S$	27.7	27.7				
15b	H	2-Thiazolyl[f,j,k]	194–196	$C_5H_{10}ClN_3O_2S_2$	26.3[c]	26.4				
16b	H	2-(1,3,4-Thiadiazolyl)[e]	207–208.5 (dec.)	$C_4H_8N_4O_2S_2$	26.9	26.7	30.8[c]	30.7		
17b	H	Phenyl[f]	123–125	$C_8H_{12}N_2O_2S$	14.0	13.9				
18b	H	4-Chlorophenyl[d]	160.5–161.5	$C_8H_{11}ClN_2O_2S$	11.9	11.8				
19b	H	3,5-Dibromophenyl[f]	155–157	$C_8H_{10}Br_2N_2O_2S$	7.8	7.8				
20b	H	4-Tolyl[f]	129–130.5	$C_9H_{14}N_2O_2S$	13.1	12.9				
21b	H	4-Sulfamylphenyl[e]	186–187 (dec.)	$C_8H_{13}N_3O_4S_2$	15.0	14.9				
22b	H	4-Methoxyphenyl[d]	177–178	$C_9H_{14}N_2O_3S$			46.9	47.1	6.1	6.2
23b	H	4-Carboxyphenyl[d,i]	249–257 (dec.)	$C_9H_{12}N_2O_4S$	11.5	11.4				
24b	H	4-Nitrophenyl[b]	214–218 (dec.)	$C_8H_{11}N_3O_4S\cdot H_2O$			36.5	36.8	5.0	5.0
25b	Et	Phenyl[f]	118–119 (dec.)	$C_{10}H_{17}ClN_2O_2S$	10.6	10.6				
26b	H	2-Naphthyl[e]	162.5–163.5	$C_{12}H_{14}N_2O_2S$	11.2	11.2				
27b	H	Benzyl[g,j]	180.5–182.5	$C_9H_{15}ClN_2O_2S$			43.1	43.2	6.0	6.0
28b	H	2-Quinolyl[e]	177–178 (dec.)	$C_{11}H_{13}N_3O_2S$	16.7	16.8	52.6	52.6	5.2	5.3

[a] Previously prepared by Miller, *et al.*, THIS JOURNAL, 62, 2100 (1940). [b] Obtained as the hydrate. [c] Sulfur analysis. [d] Recrystallized from water. [e] Aqueous alcohol. [f] Ethanol. [g] Ethanol–benzene. [h] Carbon tetrachloride–ethanol. [i] Isopropanol–carbon tetrachloride. [j] Hydrochloride. [k] Previously prepared by Mead, *et al.*[6]

dissolved in 670 cc. of warm 15% acetic acid. The solution was refluxed for thirty minutes to cyclize the phthalamic acid. On cooling, a first crop of product was obtained. The aqueous supernatant gave a precipitate on standing overnight. This was filtered off, dissolved in the acetic acid mother liquor from the first crop and refluxed for one hour. On cooling a second crop of product was obtained. The combined crops weighed 59.1 g.

N-[2-(Benzylsulfamyl)-ethyl]-phthalamic Acid (No. 22a).—The condensation of 2-phthalimidoethanesulfonyl chloride with benzylamine by Procedure A gave a poor yield of product. The following procedure using acetone as a reaction medium was satisfactory:

A stirred suspension of 82.3 g. (0.30 mole) of the sulfonyl chloride in 300 cc. of acetone was cooled in an ice-bath and 68 cc. (0.62 mole) of benzylamine added in one portion. A vigorous reaction occurred. The creamy reaction mixture was stirred for an hour in an ice-bath, finally forming a non-stirrable paste. After standing for four hours at room temperature, the reaction mixture was mixed with 1.2 liters of water, acidified with dilute hydrochloric acid and chilled. The product was filtered, suspended in 1.2 liters of water and treated with 60 cc. of 6 *N* sodium hydroxide. After standing for fifteen minutes, 10 g. of base-insoluble material was filtered off. The filtrate was decolorized with Darco G-60, and acidified in the cold with concentrated hydrochloric acid to *p*H 2. The gum which separated crystallized readily to give 80.3 g. of white product melting at 138–139°. The base-insoluble fraction was retreated with dilute sodium hydroxide solution and gave an additional 9.5 g. of product melting at 140–142°. Both fractions were soluble in bicarbonate. When refluxed with dilute acetic acid, a bicarbonate-insoluble substance, presumably 2-phthalimidoethylsulfonobenzylamide, melting at 117–118°, was formed. Hydrazine cleavage of the phthalamic acid proceeded normally, however.

Hydrazine Cleavage. Procedure B.—A stirred suspension or solution of one mole of the substituted 2-phthalimidoethanesulfonamide in five to eight volumes of 95% ethanol was treated with one mole of 85% aqueous hydrazine hydrate. The mixture was refluxed with stirring for three hours. In most cases complete solution occurred after heating for ten minutes followed shortly by formation of a heavy white precipitate, probably the phthalhydrazide salt of the substituted 2-aminoethylsulfonamide. With the more alcohol-insoluble phthalimido compounds, complete solution did not occur at any time. A Hershberg stirrer was preferred in many cases because of the pasty consistency of the reaction mixture. The alcohol was removed by vacuum distillation, the crystalline residue suspended in warm water and acidified to congo red with the minimum amount of dilute hydrochloric acid. Heating with strong hydrochloric acid as suggested by Ing and Manske[8] is unnecessary since the amine is apparently only combined as the insoluble phthalhydrazide salt. After stirring for about ten minutes, the mixture was cooled and the insoluble phthalhydrazide filtered off. The filtrate was decolorized with charcoal if necessary. If the substituted 2-aminoethylsulfonamide was insoluble in water, careful neutralization of the acidic solution to *p*H 8 or 9 gave the free base (nos. 5b, 7b, 11b, 12b, 18b, 19b, 22b, 23b, 24b, 26b). If the free base was water-soluble (nos. 1b, 2b, 3b, 14b, 15b, 16b, 17b, 20b)

the aqueous solution of the hydrochloride was concentrated to dryness. The hydrochloride was then purified by recrystallization from some suitable solvent, usually alcohol or aqueous alcohol. Conversion to the free base was then effected by treatment of a boiling suspension of the hydrochloride in ethanol with one equivalent of alcoholic potassium ethoxide solution. In some cases a small amount of water was added to keep the free base in solution. The hot solution was filtered to remove potassium chloride and decolorized with charcoal. In most cases the free base separated on cooling. If not, the alcohol was removed and the residue recrystallized from some other suitable solvent (Table IV). The yields varied from 70 to 95%.

2-(2-Aminoethylsulfonamido)-thiazole (No. 15b).—In the attempted hydrazine cleavage of the 2-aminothiazole derivative (no. 9a) ammonia and hydrogen sulfide were evolved.[7] This observation was not unexpected since an unsuccessful attempt to hydrolyze the analogous 2-(N^4-phthaloyl-4-homosulfanilamido)-thiazole by means of hydrazine has been reported.[25] The cleavage may also be effected with alcoholic sodium hydroxide.[7] When the reaction was conducted at a lower temperature in 50% ethanol the desired product was obtained. To a refluxing suspension of 20.8 g. (0.062 mole) of no. 9a in 370 cc. of 50% ethanol, 3.7 cc. (0.063 mole) of 85% aqueous hydrazine was added. Refluxing for five minutes resulted in almost complete solution. The mixture was then heated for six hours in an oil-bath at 65°. The solvent was removed by vacuum distillation, the residue suspended in 150 cc. of water and acidified to congo red with hydrochloric acid. The yellow mixture was warmed several minutes on the steam-bath, chilled and filtered from 10.7 g. of phthalhydrazide. The filtrate was decolorized with Norit A and vacuum concentrated to a small volume. The brown solution contained some insoluble material which was filtered off and discarded. The filtrate was concentrated to a brown gum which crystallized when refluxed with 250 cc. of absolute ethanol. The alcohol was decanted and the remainder of the residue almost completely dissolved when refluxed with a fresh portion of 200 cc. of ethanol. The combined alcoholic extracts were decolorized with Norit A and chilled. The yellow solution deposited 8.9 g. of product which was recrystallized from 400 cc. of absolute ethanol to yield 6.4 g. of pure material melting at 194–195°.

(2-Aminoethylsulfono)-4-carboxyanilide (No. 23b).—Hydrazine cleavage of no. 18a using one mole of hydrazine hydrate resulted in a very small yield of product. Increasing the amount of hydrazine to two moles resulted in an improvement but reaction was still incomplete.

A mixture of 72.7 g. (0.194 mole) of no. 18a, 23.4 cc. (0.398 mole) of 85% aqueous hydrazine hydrate and 730 cc. of 95% ethanol was stirred and refluxed for three hours. The starting material almost completely dissolved and a heavy precipitate formed. The alcohol was removed *in vacuo*, the residue suspended in 600 cc. of hot water, acidified with 36 cc. of concentrated hydrochloric acid, chilled and filtered. The filtrate was treated with Norit A and neutralized to *p*H 4–5 with 8.5 cc. of 10 *N* sodium hydroxide. The resulting white flaky precipitate was filtered off, washed with water and dried to give 15.4 g. of product. The acid-insoluble material, consisting of phthalhydrazide and unreacted starting compound, weighed 64.4 g. A second treatment with 17.3 cc. of hydrazine hydrate, as before, gave 11.2 g. more of product. The acid-insoluble fraction in this case was recrystallized from 1.25 liters of 80% acetic acid. The phthalhydrazide separated on cooling to room temperature. The filtrate was concentrated to dryness *in vacuo* and the residue extracted with dilute hydrochloric acid. Neutralization to *p*H 5 gave a third crop for a total crude yield of 37.7 g. Purification by Darco G-60 treatment in dilute base followed by neutralization gave 35.7 g. (75%) of pure product.

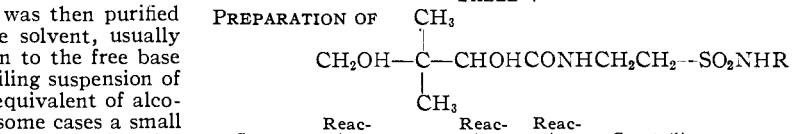
Condensation of Pantolactone with Aminoethylsulfonamides (Table V). Procedure C.—The following procedure was found to be applicable to all mono-substituted 2-aminoethylsulfonamides. One mole of the sulfonamide was dissolved in absolute alcohol containing one equivalent of potassium ethoxide. After refluxing for one-half hour to ensure complete potassium salt formation, one to two moles of pantolactone was added and the mixture refluxed for four hours. If the 2-aminoethylsulfonamide hydrochloride was used, two equivalents of potassium were necessary and the insoluble potassium chloride filtered off before the addition of the lactone. In several cases the potassium salts of the sulfonamides (5b, 7b, 21b, 23b, 24b) precipitated from the reaction mixture. It was then necessary to add the lactone in several portions and to lengthen the reaction time. In one case when an excess of potassium ethoxide was present, a racemic product resulted. Several attempts to condense the monopotassium salt of (2-aminoethylsulfono)-4-sulfamylanilide with *d*-pantolactone gave a poor yield of racemic product. The use of 1.8 equivalents of potassium raised the yield, but racemization still occurred. This may have been due either to the presence of potassium ethoxide arising from the equilibrium, $-SO_2NHK + C_2H_5OH \rightleftarrows -SO_2NH_2 + C_2H_5OK$, or to the inherent basicity of the potassium salt of the weakly acidic unsubstituted sulfamyl group.

After the reaction was completed, the alcohol was removed by room temperature vacuum concentration and the viscous residue dissolved in cold water. The solution was then exactly neutralized with one equivalent of acetic or hydrochloric acid. The product, which in some cases separated as a gummy mass, could usually be induced to crystallize by seeding and triturating. After removal of the aqueous phase, the crude product was dried and recrystallized from a suitable solvent (Table V).

Procedure D.—For the 2-aminoethylsulfonamides melting below 180°, fusion with the lactone for one or two

TABLE V

PREPARATION OF



Compound no.[f]	Reaction procedure	Molar ratio[a]	Reaction time, hr.	Reaction temp. °C.	Crystallization solvent[c]	Yield, %
1	D[b]	1.1	48	20		
2, 3, 4	D	2.0	1.5	100	EA30-E5	60
6	C	1.5	4.0		W20	73
7	C	1.5	5.0		W18	65
8	C[d]	1.5	5.0		E5-WO.2	41
9	C	1.7	15		W11	50
10	C	1.5	24		W14	53
11	D[e]	2.0	2.0	105		62
12	D	2.0	2.0	110	B12-EA3	54
13	D	1.4	2.0	105	M3.4-W6.6	71
14, 15, 16	D	1.6	1.3	110	ED-4	70
17	D	2.0	1.5	110	B15-EA1	85
18	C	2.0	14		W5	51
19	D	2.0	2.0	110	ED-20	70
20	C	1.5	77		B80-EA80	21
21	C	2.0	69		EA12	58
23	D	1.0	2.5	80	W65	55
24	C	1.5	4.0		E15-W45	60
25	D	1.5	1.5	65	B20-EA6	37

[a] Pantolactone/aminoethylsulfonamide. [b] Isolated by distillation, bath temperature 130°/10^{-7} mm. [c] EA, ethyl acetate, E, ethanol, B, benzene, C, chloroform, ED, ethylene chloride, M, methanol, W, water. Volume in ml. of solvent or mixed solvent required for 1.0 g. of material. [d] Crystallized directly from the reaction mixture on neutralizing with acetic acid. [e] Obtained as an amorphous solid by precipitation from ethyl acetate solution with ether. [f] Refers to Compound No. in Table I.

(25) Bergeim and Braker, THIS JOURNAL, **66**, 1459 (1944).

hours at a temperature of about 100° was found preferable for reasons of simplicity. The melts were stirred until complete solution of the sulfonamides occurred. If the hydrochloride of the sulfonamide was used as the starting material, the free base was obtained by treatment with one equivalent of alcoholic potassium ethoxide, filtration to remove potassium chloride, and vacuum concentration. Procedure D was found to be inapplicable to 2-aminoethylsulfonamides melting above 180°. After the reaction was completed, the melts were dissolved in a suitable solvent mixture (Table V) and crystallization facilitated by seeding. Many of the final products were obtained crystalline only with great difficulty, having a pronounced tendency to form supersaturated solutions or to separate as an oil even when seeded and cooled slowly. The pantoyl derivatives of compounds 14b, 15b and 16b could not be obtained in a crystalline state. The *l* and *dl* isomers reported in Table I were prepared from *l* and *dl*-pantolactone, respectively.

Diacetate of d-2-[2-(Pantoylamino)-ethylsulfonamido]-pyridine (No. 5).—A suspension of 10.0 g. (0.0301 mole) of no. 3 in 12.0 cc. of dry pyridine was stirred and treated dropwise over a twenty-minute period with 8.1 g. (0.08 mole) of acetic anhydride. The temperature rose to 70° and was held there for two hours by heating in an oil-bath. After cooling, 20 cc. of absolute ethanol was added and the reaction mixture vacuum concentrated to a viscous oil. Three additional 10-cc. portions of alcohol were added and distilled off. Seeding during this process led to a crystalline residue which was pulverized under 20 cc. of cold water and filtered. The 10.3 g. of crude product was recrystallized twice from 40 cc. of water. A yield of 9.1 g. of pure No. 5 resulted.

***d*-[2-(Pantoylamino)-ethylsulfono]-4-aminoanilide (No. 22).**—A solution of 15.0 g. of no. 21 in 150 cc. of acetone was reduced rapidly at an initial pressure of 55 lb. in the presence of 0.3 g. of Adams catalyst. The reduction was carried out in duplicate. The bright yellow filtrates were combined and vacuum concentrated. The residual gum was dissolved in 75.0 cc. of ethyl acetate; crystallization was spontaneous. Filtration gave 26.8 g. (97%) of yellow product, m. p. 136.5–139°. Recrystallization gave 20.5 g. of pure product.

N-Butyryltaurine Sodium Salt.—Seven grams (0.056 mole) of taurine in 40 cc. (0.255 mole) of butyric anhydride was heated in a metal bath at 135–140° for nineteen hours. The solution was decanted from the gummy precipitate and diluted to 475 cc. volume with petroleum ether. The residue was treated with 50 cc. of 95% alcohol and the solution filtered from 4.7 g. of unreacted taurine. The petroleum ether solution was decanted from the gummy residue which had settled out on standing. This residue was dissolved in the alcohol filtrate and the whole refluxed with Norit for two hours and filtered. The filtrate was concentrated and then filtered from a small amount of taurine. The solution was again diluted with petroleum ether to remove any butyric anhydride and to precipitate butyryltaurine. The residue which separated was dissolved in alcohol and treated with alcohol in which 0.18 g. (0.008 g. atom.) of sodium had reacted. The addition of dioxane and heating of the mixture on a steam-bath for one hour yielded a precipitate which could be filtered. The sodium salt could be recrystallized either from this solvent mixture or from 95% alcohol; final m. p. 268–270°.

Anal. Calcd. for $C_6H_{12}NaNO_4S$: Na, 10.6. Found: Na, 10.9.

N-Butyryl-β-alanine Sodium salt.—Fifteen grams (0.168 mole) of β-alanine in 30 cc. (0.191 mole) of butyric anhydride was warmed on a steam-bath for seven hours. The mixture was cooled and the addition of petroleum ether or diethyl ether resulted in the separation of an oil which solidified on standing in the refrigerator. A first crop of 15.0 g. of product, m. p. 50–60°, was obtained. Further dilution of the filtrate with petroleum ether and cooling gave 5.6 g. of additional product, m. p. 61–63°, with sintering at 57°. This represents a total crude yield of 77%.

Five and six-tenths grams (0.037 mole) of butyryl-β-alanine was dissolved in 25 cc. of 95% alcohol and treated with 0.84 g. (0.0365 g. atom.) of sodium dissolved in 25 cc. of absolute alcohol. On standing, 4.6 g. of the sodium salt was obtained. After recrystallizations from alcohol, the final m. p. was 220–222°.

Anal. Calcd. for $C_7H_{12}NaNO_3$: N, 7.7; Na, 12.7. Found: N, 7.7; Na, 12.6.

N-(γ-Hydroxybutyryl)-β-alanine Sodium Salt.[28]—Eight and five-tenths grams (0.099 mole) of redistilled γ-butyrolactone and 7.45 g. (0.067 mole) of sodium β-alanine were mixed in 25 cc. of absolute methanol (dried over barium oxide and distilled from Drierite) and refluxed for eight hours on the steam-bath. The solution was filtered hot, and on cooling 11.2 g. of product (85% crude yield) melting at 115–150° crystallized from the solution. Recrystallization from a 2:1 mixture of isopropyl and methyl alcohols gave a final product melting at 152.5–155°.

Anal. Calcd. for $C_7H_{12}NaNO_4$: N, 7.1; Na, 11.7. Found: N, 7.0; Na, 11.9.

N-(γ-Hydroxybutyryl)-taurine Sodium Salt.—Eight and five-tenths grams (0.099 mole) of redistilled γ-butyrolactone and 9.85 g. (0.067 mole) of the sodium salt of taurine were refluxed with 100 cc. of absolute ethanol for fourteen hours. On cooling the reaction mixture and concentrating, 13.8 g. of crude product was obtained. By fractional crystallization using a mixture of methanol and isopropanol (17 cc. methanol and 2.3 cc. isopropanol per gram) a small amount of constant melting product, m. p. 212–214°, was obtained.

Anal. Calcd. for $C_6H_{12}NaNO_5S$: N, 6.0; Na, 9.9. Found: N, 6.2; Na, 10.1.

N-(α,γ-Dihydroxybutyryl)-taurine Sodium Salt.—α-Hydroxy-γ-butyrolactone was prepared from acrolein using literature procedures.[27] A solution of 4.83 g. (0.33 mole) of the sodium salt of taurine in 75 cc. of absolute methanol was treated with 6.75 g. (0.0655 mole) of α-hydroxy-γ-butyrolactone. The solution was refluxed for forty-three hours. Concentration of the solution yielded 8.2 g. (58%) of crude product. This was fractionally recrystallized from methanol to yield 0.9 g., m. p. 153.5–156°.

Anal. Calcd. for $C_6H_{12}NaNO_6S$: N, 5.6; Na, 9.2. Found: N, 5.5; Na, 9.5.

Summary

A number of new amides of pantoyltaurine and several other related compounds have been prepared.

The antibacterial, antimalarial activity and pantothenic acid reversibility of these substances are recorded.

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(27) Glattfeld and Sander, THIS JOURNAL, **43**, 2675 (1921). Carter and May, *ibid.*, **63**, 312 (1941).